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| 10/517,980 | 12/13/2004 | James P. Landers | 00776-03 | 1947 |

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UNIVERSITY OF VIRGINIA PATENT FOUNDATION
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| EXAMINER | |
|---|---|
| KINGAN, TIMOTHY G | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| *Office Action Summary* | **Application No.** | **Applicant(s)** | |
|---|---|---|---|
| | 10/517,980 | LANDERS ET AL. | |
| | **Examiner** | **Art Unit** | |
| | TIMOTHY G. KINGAN | 1797 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on _13 December 2004_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) _1-22_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1-22_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _13 December 2004_ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

   1. Determining the scope and contents of the prior art.
   2. Ascertaining the differences between the prior art and the claims at issue.
   3. Resolving the level of ordinary skill in the pertinent art.
   4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over M. Knapp et al., U.S, Patent 6,235,471 (herein after Knapp) in view of Q. Tang and M.L. Lee, J. Chromatography A, 887:265-275, 2000 (herein after Tang).

For Claim 1, Knapp teaches a number of microfluidic devices manufactured on a substrate (body structure) (col 5, lines 7-10) with at least a first reaction channel and introduction channel (col 5, lines 7-9) (microchannel and inlet port), and that fluid flows across a channel by applying a potential across ports connecting the channel (col 47, lines 47-50). From such connection of channels with wells it would be obvious to one of ordinary skill that wells are fully capable of functioning as outlet as well as inlet ports.

Further, reagent introduction channels (wells) are machined on the substrate (col 5, lines 7-10) (on exterior surface).

Knapp does not teach a sol-gel matrix in the microchannel. Tang teaches sol-gel bonded particles (matrix) in a capillary column (abstract) (spans cross section of microchannel). One of ordinary skill in the art at the time of invention would have found desirable the use of the sol-gel matrix of Tang, comprising well-characterized chemistry for its production with readily available reagents, in the microchannel environment of Knapp, to immobilize particles in order to retain the high plate number of such small particles, while avoiding the difficulty associated with the requirement for frits during packing of particles.

For Claim 2, Tang teaches silica particles in the sol-gel matrix (abstract).

For Claim 3, Knapp teaches microfluidic devices having reaction channels and/or chambers (col 9, lines 59-61), and that reagents may be delivered to such chambers (col 12, lines 30-33) (in communication with an outlet port).

For Claim 4, Knapp is silent on use of tetramethoxy orthosilicate monomers in preparation of sol-gels. Tang teaches use of tetramethoxysilane (tetramethoxy orthosilicate) in preparation of sol-gels (p. 267, col 2, ¶ 1). Such precursors are known in the art, and one of ordinary skill in the art would find obvious the use of the chemistry teaching of Tang with the microfluidic device of Knapp in order to provide a matrix of predictable immobilized packing phase with the bed stability of sol-gels. It would have been obvious to one of ordinary skill in the art to modify the device of Knapp by substituting the sol-gel matrix of Tang in order to . . .

4. Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp and Tang as applied to claim 1 above, and further in view of S. Sato et al., J. of Materials Science, 25:4880-4885, 1990 (herein after Sato).

For Claim 5, Knapp and Tang are silent on matrix pore sizes. Sato teaches control of pore size distribution through sol-gel process (title) and further teaches pores sizes of ca. 1 micron obtained with certain additives (p. 4883, col 2, ¶ 3). One of ordinary skill in the art at the time of invention would find obvious the use of additives disclosed in the teaching of Sato in combination with the sol-gel and microfluidics of Tang and Knapp in order to impart a range of flow rates and to limit back pressure associated with the smallest pore sizes.

For Claim 6, Sato teaches control of pore size distribution through sol-gel process (title) and further teaches pores sizes of ca. 1 micron obtained with certain additives (p. 4883, col 2, ¶ 3), within the range of the instant claim.

For Claim 7, Tang teaches that particles of the sol-gel bed (matrix) are bonded to the inner walls of the capillaries (p. 268, ¶ 2) (microchannels).

For Claim 8, Knapp, Tang and Sato are silent on the filling of microchannels from first to second end. One of ordinary skill in the art at the time of invention would find useful the filling of channels from end to end in order to simplify the process of construction of the matrix, since the channel could be filled to overflow, followed by cleaning of inlet and outlet ports, without concern for variability in the fill from one device to the next and without the need for frits.

4. Claims 9-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over L.A. Christel, et al., J. Biomechanical Engineering, 121: 22-27. 1999 (herein after Christel) in view of Tang.

For Claim 9, Christel teaches use of nucleic acid capture chips in which DNA (sample) solutions are diluted with (contacted with) a binding agent/chaotropic salt (chaotropic agent) (p. 24, ¶ 2-3), passed through the microstructure (microcolumn) under conditions in which DNA (nucleic acid) binds (p. 24, ¶ 3). Christel does not teach a sol-gel matrix. Tang teaches a sol-gel matrix comprising silica particles bonded with octadecyl and propylsulfonic acid functional groups. One of ordinary skill in the art at the time of invention would find desirable the use of unbonded silica particles, as an alternative to and extension of use of particles with a bonded phase, in order to expand the range of analytes that can be concentrated and purified with such sol-gel matrices to nucleic acids. It would have been obvious to one having ordinary skill in the art to modify the method of Christel to employ the sol-gel matrix of Tang with unbonded silica in order to extract and purify DNA with well-characterized chemistry and solvent systems in a stable bed environment. With regard to the cross sectional dimension, Tang teaches use of capillaries of 75 microns inner diameter, within the cross sectional range of the instant claim.

Christel further teaches the steps of washing the microstructure with ethanol-based wash (a solvent) and eluting with elution reagent (p. 24, col 2, ¶ 1) (releasing bound nucleic acid).

For Claim 10, Tang teaches the use of capillaries containing sol-gel matrix of 75 microns inner diameter (1406 microns$^2$ cross sectional area, within that of the instant claim).

For Claim 11, Christel teaches the use silicon microstructures as nucleic acid (DNA) capture chips (p. 24, ¶ 2).

For Claim 13, Christel teaches the steps of washing the microstructure with ethanol-based wash (a buffer) intended to wash away salts and other PCR inhibitors (p. 24, col 2, ¶ 1). The elution of DNA that follows, such as with water (p. 24, col 1, ¶ 2), would be recognized by one of ordinary skill in the art to be compatible with PCR reactions.

5. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Christel and Tang as applied to claim 9 above, and further in view of Sato. Christel and Tang are silent on pore sizes in a sol-gel matrix. Sato teaches that such pore sizes can be controlled (abstract) and further that pores sizes of ca. 1 micron diameter are obtained with certain additives (p. 4883, col 2, ¶ 3), a size within the range of the instant claim. It would have been obvious to one having ordinary skill in the art to employ the specific controlled pore size taught by Sato in order to impart a range of flow rates and to limit back pressure associated with the smallest pore sizes.

7. Claims 14-18 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp in view of Tang.

For Claim 14, Knapp teaches a number of microfluidic devices manufactured on a substrate (base) (col 5, lines 7-10). Such devices may have a first and second reaction microchannel each having an interior surface and first and second end (Fig. 21). Further, Knapp teaches a first opening (port) in communication with the first end of the first microchannel (Fig. 21). Knapp does not teach a second port in communication with the second end of the first channel and the first end of the second channel or a third port in communication with the second microchannel. However, Knapp teaches that such devices may have hundreds of reaction channels (microchannels) with reagent introduction channels (ports), and that fluid may flow between the channels under selected conditions (col 5, lines 10-17). One of ordinary skill in the art at the time of invention would recognize the desirability of a second port in communication with two or more channels in order to allow for separate introduction of multiple reagents that subsequently combine in a reactive process, or in order to allow for overflow after introduction into one port and escape of overflow from a second port. Further, one of ordinary skill would find obvious to use a third port in order to allow additional flexibility associated with reactive processes requiring introduction of multiple reagents.

With regard to a sol-gel matrix, Knapp does not teach such matrix in the microchannel. Tang teaches sol-gel bonded particles in a capillary column (abstract) (spans cross section of microchannel). It would have been obvious to one of ordinary skill in the art at the time of invention to use the sol-gel matrix of Tang, comprising well-characterized chemistry with readily available reagents, in the microchannel environment of Knapp, in order to immobilize particles and retain the high plate number

of such small particles, while avoiding the difficulty associated with the requirement for frits during packing.

For Claim 15, Knapp teaches a microfluidic device with at least one reaction channel or chamber (col 9, lines 59-61) (chamber in communication with channel) and that such chamber may be widened (col 32, lines 30-32). Knapp further teaches that such devices may comprise networks of channels (col 13, line 11-13). One of ordinary skill in the art at the time of invention would find obvious from the teaching of Knapp the desirability of the reaction chamber being in contact with the microchannels for independent introduction of reagents to the chamber.

For Claim 16, Knapp and Tang are silent on three ports on the same exterior surface. Knapp does teach that channels are fabricated into the surface (same surface) of the substrate (col 51, lines 13-14). One of ordinary skill in the art would find obvious from the teachings of Knapp to form ports on the same exterior surface in order to facilitate delivery of reagents with minimal operator handling of the device during such operation.

For Claim 17, Knapp teaches that material transport in a microfluidic device is accomplished with micro-pumps (col 5, lines 20-25) (pumping means in communication with chamber).

For Claim 18, Knapp teaches that reagents are pumped into the main channel of the microfluidic device (col 22, lines 64-65), and, more generally, that selective flowing and movement of fluids through the device (channels and chambers) is accomplished with micropumps (pumping means) (col 50, lines 51-57). One of ordinary skill in the art

would find obvious from these teachings the potential for use of such pumps for regulating flow through first and second microchannels.

For Claim 20, Tang teaches that particles of the sol-gel bed (matrix) are bonded to the inner walls of the capillaries (p. 268, ¶ 2) (microchannels). It would have been obvious to one of ordinary skill in the art to modify the column of Knapp to bond the particles to the inner wall of the microchannel in order to ensure no loss of matrix during processing.

For Claim 21, Knapp teaches the addition of template DNA, such as from a cloned nucleic acid, into a reaction channel of a microfluidic device (col 14, lines 16-24) and sequencing reagents are subsequently added (col 14, lines 30-31). One of ordinary skill in the art at the time of invention would have found obvious to use the second microchannel for such sequencing reagents (for analyzing nucleic acids) in order to physically separate the steps of introducing other reagents, such as templates, to minimize the likelihood of contamination.

For Claim 22, Knapp teaches a microfluidic device is fabricated into a planar solid substrate (col 42, lines 16-18) (base) and that such device is used for biochemical analysis, including purification of nucleic acids (abstract) (nucleic acid processing).

8. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp and Tang as applied to claim 18 above, and further in view of Sato.

Knapp and Tang are silent on pore sizes in a sol-gel matrix. Sato teaches that such pore sizes can be controlled (abstract) and further that pores sizes of ca. 1 micron are

obtained with certain use of certain additives during matrix formation (p. 4883, col 2, ¶ 3), a size within the range of the instant claim. Again, it would have been obvious to one having ordinary skill in the art to modify the device of Knapp and Tang to provide a control pore size of about 1 micron as taught by Sato in order to impart a range of flow rates and to limit back pressure associated with the smallest pore sizes.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jill Warden/
Supervisory Patent Examiner, Art Unit 1797

TGK